group consisting of circulating microparticles, stimulated procoagulant cells and mixtures thereof;

mixing the sample containing said member with a purified receptor specific for a phospholipid, under conditions to form a complex of the purified receptor and said member, wherein said purified receptor is bound to a solid phase,

removing unbound components;

determining any complex bound to said solid phase; as an indication of an individual's prethrombotic state; and

comparing the individual's prethrombotic state to prethrombotic values associated with an assortment of diseases and risk factors, thereby screening for disease and identifying risk factors.

REMARKS

In the Office Action dated October 31, 2001, claims 36-44, 64 and 65, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks.

Claims 36-44 and 64-65 were rejected under 35 USC §112, first paragraph, as lacking an enabling description of how a prethrombotic state is compared with prethrombotic values associated with an assortment of diseases and risk factors. Applicants respectfully point out page 6, second paragraph, to page 7, of the present specification, particularly the last paragraph on page 6, which states that it "was found

that the amount of circulating microparticles and/or stimulated procoagulant cells in the blood of an individual correlates with the prethrombotic [state] of this individual as well as with the above mentioned vascular diseases". In addition, Table 1 provides values associated with various diseases. In view of this disclosure, applicants request that this rejection be withdrawn.

Claims 36-44 and 64-65 were rejected under 35 USC §112, second paragraph as indefinite. Claim 36 has been amended to overcome this rejection. In view of these amendments, applicants request that this rejection be withdrawn.

Claims 36-38, 41, 64 and 65 were rejected under 35 USC §103(a) as unpatentable over Abrams in view of Rote and Margel. Abrams discloses a method for detecting activated platelets. However, Abrams does not suggest or disclose the use of receptors for phospholipids or phospholipid complexes. He uses antibodies to surface antigens and flow cytometry for the detection of the activated platelets. In his method, no immobilization and thus no separation of a solid phase (carrying immobilized cells) and a liquid phase is carried out. Therefore Abrams would have a high background signal which is avoided by the present invention. Rote and Margel do not cure the deficiencies in Abrams as neither Rote or Margel suggest or disclose immobilizing the microparticles or cells on a solid phase. Rote uses flow cytometric analysis to determine the reactivity of his antibodies against platelets and Margel discloses only labels for cell labeling.

The present invention makes it possible to detect a thrombotic risk or to detect a high level of cell activation (e.g. apotosis) in body fluids by taking into account the

properties of phospholipids or phospholipid complexes that are exposed on circulating microparticles or cells. The present invention uses an immobilization step on a solid phase followed by the separation of solid phase (carrying microparticles or cells) and liquid phase. This detection system permits the measurement of the amount of immobilized phospholipids based on the real in vivo procoagulant potential of the microparticles or cells that possess exposed phospholipids. The whole detection process takes place on the biological cell membrane from an activated human cell.

The capture of the activated cells or fragments thereof on a solid phase is essential to allow the separating steps to be performed. Using these steps, a high background signal is eliminated. By using antibody-dependent immobilization of cells or microparticles the present system permits the measurement of the procoagulant potential linked to a specific type of cells or microparticles that are characterized and captured through a specific membrane linked antigen.

Since neither Abrams, Rote or Margel suggest or disclose immobilization and separation of a solid phase carrying immobilized cells, the combination of these references does not suggest a method to detect a thrombotic risk which takes into account the properties of phospholipids exposed on microparticles, without a high background signal, as in the present invention. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 36-38, 41, 64 and 65 were rejected under 35 USC §103(a) as unpatentable over Abrams in view of Rote and Carriere. As discussed above, neither Abrams nor Rote suggest a method to detect a thrombotic risk which requires

immobilization and separation of a solid phase carrying immobilized cells. Though Carriere discloses solid phase immobilization and separation, he does not suggest that such a method can be used to detect stimulated procoagulant cells. Applicants respectfully point out that both of the references cited for the detection of activated platelets use flow cytometry. Abrams indicates on page 469, top of the right column, that sample washing or centrifugation may traumatize platelets and induce unwanted cell activation. Therefore, one would not combine Abrams and Rote with Carriere's solid phase method as one would not expect to accurately detect activated procoagulant cells due to in vitro cell activation caused by the solid phase separation. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 36-38, 41, 64 and 65 were rejected under 35 USC §103(a) as unpatentable over Abrams in view of Rote and Hajek and/or Harlow. Neither Hajek nor Harlow suggest that in vivo activated platelets can be accurately detected using a solid phase method. Therefore, these references do not cure the deficiencies in Abrams and Rote as discussed above. In view of these deficiencies, applicants request that this rejection be withdrawn.

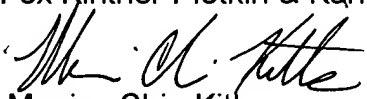
Claims 39-40 were rejected under 35 USC §103(a) as unpatentable over Abrams in view of Rote and Margel and further in view of Dachary-Prigent. Claims 39-40 were rejected under 35 USC §103(a) as unpatentable over Abrams in view of Rote and Carriere further in view of Dachary-Prigent. Claims 39-40 were rejected under 35 USC §103(a) as unpatentable over Abrams in view of Rote, Hajek and/or Harlow, and further in view of Dachary-Prigent. Abrams, Rote, Margel, Carriere, Hajek and Harlow have

the deficiencies discussed above, Dachary-Prigent does not cure these deficiencies as Dachary Prigent also uses flow cytometry to detect the activated platelets and therefore does not suggest that in vivo activated platelets can be accurately detected without unwanted in vitro activation using a solid phase method. In view of the above discussion, applicants request that these rejections be withdrawn.

Applicants respectfully submit that the application is now in condition for allowance, and request that claims 36-44, 64 and 65 be allowed.

In the event that this document is not considered to be timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to Deposit Account No. 01-2300, along with any other fees which may be required with respect to this response.

Respectfully submitted,
Arent Fox Kintner Plotkin & Kahn, PLLC



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Attachments: Petition for Extension of Time
Marked Up Copy of Claims

MARKED UP CLAIMS FOR 09/588,553

36. A method for determining [the] a prethrombotic state of an individual for [the diagnosis of] screening for disease and identification of risk factors, comprising:

obtaining a body fluid sample comprising a member selected from the group consisting of circulating microparticles, stimulated procoagulant cells and mixtures thereof;

mixing the sample containing said member with a purified receptor specific for a phospholipid, under conditions to form a complex of the purified receptor and said member, wherein said purified receptor is bound to a solid phase,

removing unbound components;

determining [the amount of said] any complex bound to said solid phase; [thereby determining the] as an indication of an individual's prethrombotic state; and

comparing the individual's prethrombotic state to prethrombotic values associated with an assortment of diseases and risk factors, thereby [diagnosing] screening for disease and identifying risk factors.